Kidney International, Vol. 28 (1985), pp. 535–540

Effects of acetate and bicarbonate dialysate in stable chronic dialysis patients

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Effects of acetate and bicarbonate dialysate in stable chronic dialysis patients. The effects of acetate and bicarbonate dialysate on the biochemical and clinical parameters of 16 stable chronic hemodialysis patients were investigated in a double-blind crossover study. A central delivery system was used for both types of dialysates with identical sodium concentrations (138 mEq/liter) and osmolality in a single-pass dialysate flow. The results indicate that dialysis with bicarbonate leads to significantly less hypoxemia ($P \leq 0.001$) and hypotensive episodes ($P \leq 0.002$) than with acetate. Pre- to post-dialysis blood pressure changes were also more marked during acetate dialysis. Older patients with recurrent hypotension on acetate benefit most from bicarbonate dialysate. This group of patients appears to metabolize acetate more slowly and has a significantly lower post-dialysis bicarbonate concentration ($P \leq 0.005$) than asymptomatic patients during dialysis with acetate dialysate.

Effet d'un dialysat avec acétate ou bicarbonate chez des hémodialysés chroniques stables. Les effets d'un dialysat avec acétate ou bicarbonate sur les paramètres biochimiques et cliniques de 16 hémodialysès stables ont été explorés par une étude croisée en double insu. Un système d'apport central a été utilisé pour les deux types de dialysats, avec des concentrations de sodium (138 mEq/liter) et une osmolalité identiques avec un flux de dialysat non recyclé. Les résultats indiquent que la dialyse avec du bicarbonate entraîne une hypoxémie ($P < 0{,}001$) et des épisodes d'hypotension ($P < 0{,}002$) significativement moindres qu'avec l'acétate. Les modifications de pressions sanguines pré- et post-dialytiques étaient également plus marquées au cours de la dialyse en acétate. Les patients les plus âgés qui avaient plus d'hypotension en acétate ont le plus bénéficié de la dialyse en bicarbonate. Ce groupe semble métaboliser l'acétate plus lentement et a une concentration de bicarbonate post-dialytique significativement plus faible ($P < 0{,}005$) que les malades asymptomatiques qui utilisent un dialysat avec de l'acétate.

Several studies have shown the beneficial effects of bicarbonate dialysate in reducing the morbidity associated with dialysis in critically ill patients [1–4]. These benefits include a lower incidence of arterial hypotension [1, 3, 4], improved left ventricular stroke work and stroke volume [2], and lower incidence of nausea, vomiting, and headache [1]. However, the advantages of using bicarbonate dialysate in stable outpatient chronic dialysis patients has been the subject of debate [5–11]. While some studies have shown a significant improvement in dialysis-associated morbidity [5–9], others have not been able to demonstrate similar improvements [10, 11]. Two confounding variables have been suggested as the cause for these discrepant results [10, 12–14]. The first is that the osmolality of the two types of dialysate used in some studies has been different, primarily due to differences in the sodium concentration. The second is that some studies have used large surface area dialyzers, allowing an influx of acetate that may have exceeded the patient's ability to metabolize it efficiently to bicarbonate [12–16]. In addition, technical difficulties in the ability to prepare bicarbonate dialysate for a central delivery system have hampered the study of inter- and intradialytic subjective symptoms in a double-blind fashion or in a large outpatient dialysis population. Bicarbonate dialysis has, therefore, been restricted to use in individual bicarbonate delivery systems, resulting in markedly higher per-treatment costs.

The recent introduction of a new bicarbonate dialysate preparation that can be used in central delivery systems has allowed us to investigate the differences in intra- and interdialytic morbidity in a large outpatient dialysis facility in a double-blind crossover study using "high" dialysate sodium concentration. The results of our study indicate that bicarbonate dialysate can be prepared easily for central delivery, and that its use improves intradialytic symptoms and interdialytic well-being in this outpatient population, particularly in a subset of patients with recurrent intradialytic hypotension.

Methods

Sixteen patients constituting an entire dialysis shift at the West Surburban Artifical Kidney Center (Framingham, Massachusetts, USA) were asked to participate in the study and informed consent was obtained. All were chronic stable outpatient dialysis patients and were free of recent hospitalizations and any evidence for recent or current symptoms of fluid overload or cardio-respiratory diseases. The characteristics of these patients are listed in Table 1. Six of the 16 patients (indicated with an asterisk in Table 1) experienced recurrent symptomatic hypotension during many of their previous dialyses. These six patients were older (mean age 69.8 ± 7.8 yrs; range 55 to 77 yrs) than non-symptomatic patients (mean age 59.9 ± 12.9 yrs; range 41 to 81 years), but were otherwise not different in the etiology of renal disease or associated medical condition such as diabetes or heart disease.

The study period duration was 3 months. During the first month, patients were dialyzed with acetate dialysate; this was

Received for publication November 15, 1984,
and in revised form February 15, 1985

Table 1. Clinical characteristics of patients

Patient	Age	Sex	Treatment time, *hours*	Time on dialysis, *months*	Renal diagnosis	Associated diagnosis
*DA	77	F	4.0	14	GN	Diabetes
SB	61	M	4.5	26	GN	Angina
MB	59	F	4.0	29	Nephrosclerosis	—
*CB	70	F	4.0	8	Nephrosclerosis	—
GC	81	M	5.0	> 100	Pylo	—
DC	61	F	4.0	79	PCKD	—
LC	40	F	5.0	40	SLE	—
*MH	73	F	4.0	27	Papillary necrosis	Pacemaker
LH	73	M	4.0	> 100	GN	Peripheral vascular disease
LK	41	F	4.5	32	Nephrosclerosis	—
*AL	55	M	4.0	23	Nephrosclerosis	—
*JM	75	M	4.5	18	Nephrosclerosis	—
CR	66	M	4.0	46	GN	Angina
HS	65	F	4.5	> 100	PCKD	—
GS	52	F	4.0	54	GN	—
*AT	69	M	4.0	8	Interstitial nephritis	—

Abbreviations are: *, symtomatic patients; GN, presumed glomerulonephritis; Pylo, chronic pylonephritis; PCKD, polycystic kidney disease; SLE, systemic lupus erythematosis.

Table 2. Dialysate composition

	Acetate	Bicarbonate
Na, *mEq/liter*	138	138
Cl, *mEq/liter*	104	105
K, *mEq/liter*	2.0	2.0
Ca, *mEq/liter*	3.5	3.5
Mg, *mEq/liter*	1.5	1.5
Acetate, *mEq/liter*	41	4.0
HCO_3, *mEq/liter*	—	36
Dextrose, *mg/dl*	100	100

followed by a month on bicarbonate dialysate. Subsequently, all patients were returned back to acetate dialysis for a third month. The composition of the dialysate in each phase of the study is shown in Table 2. The nominal and the measured sodium concentration and osmolalities of both dialysates were identical (Technicon autoanalyzer, Massachusetts, USA).

A bicarbonate central delivery system (Centralyte, Erika Inc., Rockleigh, New Jersey) was used in the study. The dialysate was supplied in two components, an acid concentrate containing calcium chloride, magnesium chloride, acetic acid, and water and a powder (dry pack) containing sodium chloride, sodium bicarbonate, potassium chloride, and dextrose. The concentration of these components is such that when mixed with reverse osmosis water, the final concentration is as shown in Table 2. Separate conductivity as well as pH meters were used to monitor the appropriate concentration of the dialysate prior to delivery to the patient's station. To ensure the double-blind nature of the study, both types of dialysate were prepared in a separate room at times other than those during which patients and staff participating in the study were present. The central delivery storage area was also in a separate room and generally not accessible to the staff. Several trial phases of the study were conducted before initiation of the data collection phase, and the exact date of initiation of each phase of the study and the type of dialysate used was not communicated to the patients or staff. Dialysate flow was single-pass, at a flow rate of 500 ml/min. The dialyzers used were cuprophane hollow fiber dialyzers, with a surface area of $0.8m^2$ (HPF-100, Erika, Inc.). There were no changes in the patients' dialysis prescription, nor were any dietary modifications made during the study. Average dialysis time was 4.25 hrs. Blood flow was 300 ml/min. Transmembrane pressure (TMP) was calculated to achieve each patient's estimated dry weight. Patients participating in the study had no effective residual renal function.

Subjective and objective evaluation included:

a) Blood gases drawn weekly from each patient participating in the study at the beginning of dialysis, 1 hr after initiation and immediately post dialysis on room air. Bloods were drawn aneorobically in heparinized syringes, capped, and iced immediately, and analyzed within 2 hrs for pH, pO_2 and pCO_2; serum bicarbonate concentration was calculated according to the Henderson-Hasselback relationship.

b) A chemistry profile, including 20 standard chemical determinations (SMA-20), was obtained on each patient weekly at the beginning of each dialysis of the week (Monday or Tuesday).

c) The time-averaged concentration of urea (TAC_{urea}) was calculated once in each patient at the mid-period of each phase of the study by determining pre- and post-dialysis blood urea nitrogen (BUN) concentrations, C_1 and C_2, respectively, and the BUN prior to the following dialysis (C_3). TAC was calculated according to the formula [17]:

$$TAC = \frac{(C_1 + C_2)T_D + (C_2 + C_3)I_D}{2\,(T_D + I_D)}$$

Where T_D = dialysis time

I_D = interdialytic time.

d) Holter monitor. Five patients were also asked to participate in a study on the effects of different dialysate on the frequency of cardiac arrhythmias. A single 24-hr Holter monitor was done on each of these patients during each phase of the study.

e) Frequency of hypotension. The frequency of hypotension, defined prospectively as diastolic blood pressure 20 mm Hg below the pre-dialysis blood pressure, was recorded by the nursing staff. Therapy for symptomatic hypotension included

Table 3. Blood gases

	Acetate	Bicarbonate	Acetate	P_{1-2}	P_{2-3}
Pre pH	7.38 ± 0.005	7.37 ± 0.005	7.36 ± 0.006	NS	NS
Pre PO_2, *mm Hg*	93.2 ± 0.96	95.5 ± 1.08	92.1 ± 1.60	NS	NS
Pre PCO_2, *mm Hg*	35.2 ± 0.38	35.7 ± 0.47	35.9 ± 0.5	NS	NS
Pre HCO_3, *mM/liter*	20.2 ± 0.27	19.8 ± 0.29	20.2 ± 0.4	NS	NS
PO_2 at 1 hr	77.3 ± 1.36	88.6 ± 1.22	78.3 ± 1.57	0.001	0.001
PO_2 at hr/Pre PO_2	0.83 ± 0.01	0.93 ± 0.01	0.85 ± 0.02	0.001	0.001
Post PO_2	81.7 ± 1.40	88.4 ± 1.12	83.0 ± 1.48	0.001	0.004
Post PO_2/Pre PO_2	0.87 ± 0.02	0.93 ± 0.01	0.90 ± 0.02	0.01	NS
Post HCO_3, *mM/liter*	21.8 ± 0.3	24.2 ± 0.3	21.8 ± 0.3	0.001	0.001
Post PCO_2, *mm Hg*	30.9 ± 0.57	34.4 ± 0.54	32.8 ± 0.58	0.001	0.004
Post pH	7.46 ± 0.006	7.46 ± 0.005	7.43 ± 0.007	NS	0.008
Post HCO_3/Pre HCO_3	1.10 ± 0.019	1.24 ± 0.21	1.11 ± 0.027	0.001	0.001

P_{1-2}: P value for difference between first acetate dialysate phase and bicarbonate.
P_{2-3}: P value for difference between bicarbonate dialysate and second acetate phase.

Table 4. Pre-dialysis biochemical data

	Acetate	Bicarbonate	Acetate	P_{1-2}	P_{2-3}
K, *mEq/liter*	5.2 ± 0.08	5.2 ± 0.09	5.5 ± 0.11	NS	NS
TG, *mg/dl*	265 ± 21.7	265 ± 24.3	301 ± 27.8	NS	NS
Cholesterol, *mg/dl*	202 ± 6.9	202 ± 8.5	200 ± 7.8	NS	NS
Calcium, *mg/dl*	9.2 ± 0.10	9.7 ± 0.11	9.7 ± 0.12	0.0001	NS
Phosphate, *mg/dl*	4.6 ± 0.16	4.8 ± 0.14	4.5 ± 0.17	NS	NS

Mean ± SEM
Abbreviations same as Table 3.

placement of the patient in the Trendelenberg position and infusion of 0.9% saline, as determined by the nursing staff according to each patient's symptoms and blood pressure response. The volume of saline administered during each dialysis for symptomatic hypotension was recorded. Manitol or hypertonic saline were not used in the treatment of hypotension. Pre- and post-dialysis sitting blood pressures were also recorded in each patient.

f) Subjective assessment. Patients were asked to note the incidence of symptoms of nausea, vomiting, fatigue, and cramps during each dialysis.

Results are presented as mean ± SEM. Statistical analysis between different dialysis phases was determined by Student's t test and by analysis of variance.

Results

The mean of the pre-dialysis blood gases is shown in Table 3. There was no statistically significant difference in pre-dialysis pH, pO_2, pCO_2, and calculated bicarbonate between different phases of the study. However, blood gases drawn 1 hr after initiation of dialysis showed a significant difference in the pO_2 between the acetate and bicarbonate dialysate phase. Thus, during the acetate phase, patients showed a significant decrease in pO_2, with mean pO_2 at 1 hr approximately 0.83 ± 0.01 of the pre-dialysis pO_2 ($P \leq 0.001$). However, during the bicarbonate phase, the extent of hypoxemia was significantly less, with the ratio of pO_2 at 1 hr to pre-dialysis pO_2 = 0.93 ± 0.01 ($P \leq 0.001$ from the acetate phase). When patients were placed back on the acetate phase, the hypoxemia at 1 hr became evident again. The hypoxemia associated with acetate dialysate persisted throughout dialysis, with the pO_2 at the end of dialysis still showing a significant decrease from pre-dialysis values (pO_2 post/pO_2 pre = 0.87 ± 0.02 for the first acetate phase and 0.90 ± 0.02 for the second acetate phase), whereas during bicarbonate dialysate, the pO_2 remained stable throughout dialysis and was only slightly less than pre-dialysis values.

Post-dialysis pCO_2 and bicarbonate levels were also significantly different between the different dialysate phases. Thus, post-dialysis pCO_2 was lower during both acetate phases ($P \leq 0.05$ from pre-dialysis) and stable during the bicarbonate dialysis. At the end of dialysis, the serum bicarbonate was in the physiologic range (22 to 30 mEq/liter) and significantly higher than pre-dialysis during the bicarbonate phase. During the acetate phases, the serum bicarbonate level immediately post-dialysis was still below the normal range of bicarbonate concentration. The pH however was not markedly different between any of the phases pre or post dialysis.

Biochemical profile drawn pre-dialysis weekly showed no notable differences between different dialysate phases, with the exception of calcium which was significantly higher during the bicarbonate dialysate phase than during the first acetate phase (Table 4).

The number of prospectively defined intradialytic hypotensive episodes experienced by patients was, however, markedly different between acetate and bicarbonate dialysate, with all treatment parameters remaining constant (Table 5). Thus, the number of hypotensive episodes during the initial acetate dialysate phase was 111, whereas the incidence decreased to 24 during the bicarbonate phase ($P \leq 0.0002$). On the subsequent acetate phase, the number of hypotensive episodes increased to 51 episodes. When the frequency of hypotensive episodes was analyzed, the six symptomatic patients were found to account

Table 5. Number of hypotensive episodes/month

Patient	Acetate	Bicarbonate	Acetate
*1	10	7	9
2	2	1	0
3	1	2	0
*4	9	0	8
5	4	1	0
6	5	0	6
7	8	2	0
*8	12	2	5
9	9	0	1
10	2	4	0
*11	12	0	7
*12	9	1	4
13	7	0	6
14	2	2	1
15	—	1	0
*16	19	2	4
Total	111	25	51
Symptomatic patients only:	71 (64%)	12 (48%)	37 (72%)

Symbol: * symptomatic patients.

Table 6. Volume of 0.9% saline administered for hypotensive episodes/month

Patient	Acetate	Bicarbonate	Acetate
*1	1,950	1,000	1,150
2	200	200	–0–
3	350	350	–0–
*4	1,600	–0–	1,500
5	200	–0–	450
6	–0–	–0–	1,400
7	500	250	–0–
*8	2,500	750	2,500
9	750	–0–	400
10	–0–	650	–0–
*11	1,200	–0–	–0–
*12	2,300	400	650
13	750	–0–	600
14	200	600	300
15	–0–	200	–0–
*16	2,450	450	700
Total:	14,950	4,850	9,650
Symptomatic patients only:	12,000 (80%)	1,700 (35%)	6,500 (67%)

Symbol: * symptomatic patients.

for the majority of the hypotensive episodes during both acetate phases. Thus, these six patients (37% of the population) accounted for 71 episodes or 64% of the hypotensive episodes during the initial acetate phase. These symptomatic patients appear to have experienced significantly more improvement with bicarbonate dialysate than the other ten patients. Thus, their incidence of hypotensive episodes decreased from 71 during the first acetate phase to 12 episodes (48%) during the bicarbonate phase.

The amount of saline used to treat hypotension mirrored the number of hypotensive episodes. Approximately 15 liters of saline was used to counteract hypotension during the acetate dialysate phase, but only 5 liters during the bicarbonate phase and 10 liters during the subsequent acetate phase (Table 6). The six patients with more frequent hypotension received the majority of the saline during the acetate dialysate phase (12 out of a total of 15 liters), but received only 1.7 liter (35%) during the bicarbonate phase, proportional to their number in the study.

In line with the decrease in hypotensive episodes, intradialytic (pre- to post-dialysis) BP changes were higher during dialysis with acetate than with bicarbonate, particularly for the symptomatic patients. During the acetate phase, the mean decrease in systolic pressure for all patients was 22.0 ± 1.6 mm Hg and 4.6 ± 0.7 mm Hg in diastolic BP, whereas during the bicarbonate phase, the intradialytic change in BP was less: 15.6 ± 1.5 mm Hg for systolic BP and 3.4 ± 0.8 mm Hg for diastolic BP. This was statistically significant for the systolic BP only ($P \leq 0.003$). However, when considering the symptomatic patients, the difference in intradialytic BP changes were more marked: during the acetate phase, the average decrease in intradialytic systolic BP was 24.6 ± 2.3 mm Hg but only 14.3 ± 2.3 mm Hg during the bicarbonate phase ($P \leq 0.02$); similarly, diastolic BP decreased by 6.6 ± 1.3 mm Hg during the acetate phase and by only 2.6 ± 1.1 mm Hg during the bicarbonate phase ($P \leq 0.017$).

The mean time-averaged urea concentration (TAC urea) determined for all patients during each phase of the study is also shown in Table 7. It is seen that during the bicarbonate phase, TAC urea increased from 56.7 ± 3.1 mg/dl to 60.9 ± 3.1 mg/dl ($P \leq 0.05$) and decreased again with return to the acetate phase to 55.0 ± 2.8 mg/dl ($P \leq 0.03$).

Table 7. TAC_{Urea} (*mg/dl*), mean of 16 patients

Acetate	Bicarbonate	Acetate	P_{1-2}	P_{2-3}
56.7 ± 3.2	60.9 ± 3.1	55.0 ± 2.8	0.05	0.03

Abbreviations same as Table 3.

Table 8. Selected symptoms, total number of episodes during each phase

	Acetate	Bicarbonate	Acetate	P_{1-2}	P_{2-3}
Nausea	31 (17)[a]	23 (9)	28 (15)	NS	NS
Vomiting	11 (8)	6 (2)	10 (9)	NS	NS (0.02)
Cramping	32 (22)	36 (12)	13 (5)	NS	0.001

Abbreviations same as Table 3.
[a] Numbers in parentheses indicate the incidence of these episodes in symptomatic patients only.

Results of the symptoms questionnaire, shown in Table 8, showed a decrease in the number of adverse symptoms during the bicarbonate phase, particularly for the symptomatic patients. However, these changes, for the most part, were not statistically significant.

Holter monitoring showed too large an inter and intra-recording fluctuation for each patient, even though they were the average of 3 separate 24-hr recordings during each month of the study (data not shown). These large fluctuations persisted even when the recording was analyzed for only 8 hrs that spanned the dialysis procedures.

Discussion

The results of this prospective, double-blind crossover study indicate that, in chronic stable dialysis patients, bicarbonate

dialysate decreases the extent of dialysis-associated hypoxemia and improves the ability of dialysis to correct their acidosis by the end of dialysis. Bicarbonate dialysate also decreases the incidence of hypotension and the volume of saline used to treat symptomatic hypotension, particularly in some patients who are prone to acetate dialysis-associated hypotensive episodes. By implication, the number of nursing staff intervention for treatment of hypotension also decreased during the bicarbonate phase.

The increase in the incidence of hypotension noted in the study, as well as others when acetate is used, is probably multifactorial. Although the effect of acetate on cardiac contractility is controversial [2, 11, 18], most studies agree on the vasodilatory effect of acetate [19–21]. In addition, the hypoxemia associated with acetate dialysis may play a significant factor in the pathogenesis of hypotension [22–24].

Recently, other studies with similar designs did not show such a difference in hypoxemia between acetate and bicarbonate [2, 10, 33]. However, it is important to note that the dialysate delivery system in these studies consisted of a recirculating system [10], which attenuates loss of CO_2 and bicarbonate from the blood and the rate of infusion of acetate from the dialysate during the acetate phase, or employed different base and sodium concentrations [2, 33]. Single-pass dialysate delivery, as performed in this study, is the most common method of dialysate delivery.

The sensitivity of some patients to the hemodynamic effects of acetate is likely to be due to their different rates of metabolism of acetate to bicarbonate [3, 26–31] or to their sensitivity to the presence of acetate [32]. It is interesting that the six patients who seemed to have the greater incidence of hypotension were older and had significantly lower mean serum bicarbonate levels at the end of dialysis when dialyzed with acetate dialysate than the other ten patients (20.0 ± 0.77 vs. 22.9 ± 0.51, $P \leq 0.005$), suggesting a lower rate of conversion of acetate to bicarbonate in these patients. During bicarbonate dialysis, there was no difference in the post-dialysis serum bicarbonate levels between these subsets of patients. It is possible, therefore, that measurements of serum bicarbonate at the end of dialysis with acetate may indicate patients who have slow acetate metabolism and are likely to be acetate intolerant.

The increase in TAC_{urea} when there were no changes in dialytic clearance or other dialytic parameter (dialysis time, blood and dialysate flow, dialyzer type or surface area) suggests an improvement in dietary intake and represents an increase in daily protein intake of approximately 10% (0.1 g/kg/day) [17]. This is a modest increase, in line with the small increase in pre-dialysis weight and the decrease in the incidence of nausea and vomiting experienced by patients during the bicarbonate phase of the study.

The discrepancy between the results of the first acetate phase and the last acetate phase is also interesting. The frequency of hypotension and the volume of saline required during the second acetate phase was less than during the initial acetate phase. Analysis of the data of the second acetate phase also indicated that the majority of these symptoms occurred toward the second half of the month, suggesting a carryover effect of the bicarbonate phase. Recent studies have indicated that hemodialysis patients achieve a stable pre-dialysis bicarbonate concentration after 3 months of dialysis with bicarbonate dialysate, suggesting that there is a "bicarbonate buffer store" that needs to be repleted [7, 33].

In summary, the present study has documented a significant improvement in the inter- and intradialytic symptoms of patients using bicarbonate dialystate. This improvement is particularly marked in a subset of patients who may have a slower rate of metabolism of acetate. The availability of techniques for central delivery of bicarbonate should encourage its use in large outpatient dialysis facilities, since it has no significant side effects, is more sound physiologically [34, 35], and may significantly reduce the economic disadvantages of bicarbonate dialysate.

Acknowledgments

The authors would like to thank the patients and the staff of the West Suburban Kidney Center who participated in this study. This study was supported in part by the National Institutes of Health Grant HL-27041.

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